Child's Nervous System
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CASE REPORT

A boy with a congenital cerebellar mass

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Abstract

Purpose Tumorigenesis of medulloblastoma is believed to be associated with granule cell progenitor neurogenesis of the cerebellum. Nevertheless, congenital medulloblastomas are rarely found. Here, we report a case of congenital medulloblastoma that showed spontaneous albeit transient regression.

Methods A one-month-old baby presented with abnormal antenatal and postnatal imaging findings. Upon ultrasonography at 26 weeks of gestational age, Dandy-Walker malformation with vermian hypoplasia and cystic change was suspected. Brain MRI at 1 week after birth revealed gadolinium-enhancing lesions in the cerebellum with apparent infiltrative features along the cerebellar folia accompanied by three independent cysts in the upper and inferolateral sides of the lesion. Serial MRIs taken up to 5 months of age showed a decrease in the size and extent of enhancing solid portions. The baby did not show any abnormal signs or developmental delay. MRI at the age of 7 months showed enlargement of the lesion, and surgery was performed.

Results The lesion was diagnosed as medulloblastoma with histologically extensive nodularity (MBEN), genetically SHH-activated and TP53-wildtype.

Conclusion This case provides an unusual chance of observing an early phase of medulloblastoma development and raises a suspicion that medulloblastoma may initiate itself very early in cerebellar organogenesis and progress later at a certain time of postnatal development.

Keywords Congenital · Brain tumor · Medulloblastoma · Spontaneous regression

Tumorigenesis of medulloblastoma is believed to be associated with granule cell progenitor neurogenesis of the cerebellum [1]. Non-coding RNAs including Sonic Hedgehog (SHH) pathways are known to have a crucial role, which are also important for the development of the cerebellum [2]. Nevertheless, medulloblastomas are rarely found as a congenital brain tumor compared with other brain tumors, such as atypical teratoid/rhabdoid tumor (AT/RT). Moreover, congenital medulloblastomas behave unexpectedly.

Case report

A 1-month-old baby presented with abnormal antenatal and postnatal imaging findings. He was born at a gestational age (GA) of 38 weeks with a birth weight of 2950 g. He was the first baby to the parents, both of whom had no specific disease history. Upon ultrasonography at 26 weeks of GA for routine screening, cerebellar dysplasia with hyperechoic cortex was observed (Fig. 1). The hyperechoic portion grew into a large complex mass containing cysts at 33 weeks. Nevertheless, the gestational period was uneventful, and the baby was born spontaneously at full term. Brain MRI at 1 week after birth revealed gadolinium-enhancing lesions in the cerebellum with

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apparent infiltrative features along the cerebellar folia accompanied by three independent cysts in the upper and inferolateral sides of the lesion (Fig. 2). A malignant brain tumor, such as AT/RT, was the initial diagnosis based on the MRI findings. However, surgery was postponed until the baby gained more weight because the baby was too small and there were no urgent signs of hydrocephalus, increased intracranial pressure (IICP), or other neurological deficits.

Surprisingly, at the age of 3 months, MRI showed a decrease in the size and extent of enhancing solid portions, with stippled enhancement through the cerebellar surface (Fig. 2). Abdominal ultrasonography and urine metabolite analysis were performed, but no abnormal findings were obtained, so metastatic neuroblastoma was excluded from diagnosis. Gorlin syndrome was also excluded since none of the diagnostic criteria was met, such as basal cell carcinoma or intracranial calcification [3]. The baby showed no signs of systemic inflammation. Hence, a primary brain tumor could not be ruled out. Upon observing the decrease in the extent of the disease and the stability of the patient's condition, surgery was postponed, and he was followed with serial brain MRIs. The baby developed normally, with a head circumference within the normal range and no neurological deficits.

Brain MRI at the age of 5 months revealed a slight decrease in lesion infiltration compared with the last MRI. Surgery was again postponed for a short time, until MRI at the age of 7 months showed clear enlargement of both enhancing solid and cystic portions (Fig. 2). Surgery was performed. Nodular masses were connected by cysts occupying the vermis and cerebellar hemispheres. Thin tumor spreading along the cerebellar folia was noted. The lesion was well demarcated, gray colored, and hypervascular. The mass and cyst walls were almost completely removed.

Histological findings of the tumor are shown in Fig. 3. A comprehensive gene panel of 72 genomic alterations showed no alterations except a *CDH1* missense mutation (p.Met272Val, c.814A>G) (Table 1). The final diagnosis was medulloblastoma with histologically extensive nodularity (MBEN), genetically SHH activated, and TP53 wildtype.

The baby, currently at 1 year after the operation, has finished the third cycle of chemotherapy (carboplatin, etoposide, ifosfamide, vincristine, and mesna). No sign of recurrence is seen on the MRI. Although he has a mild motor development delay, he is catching up with the developmental stage appropriate for his age.

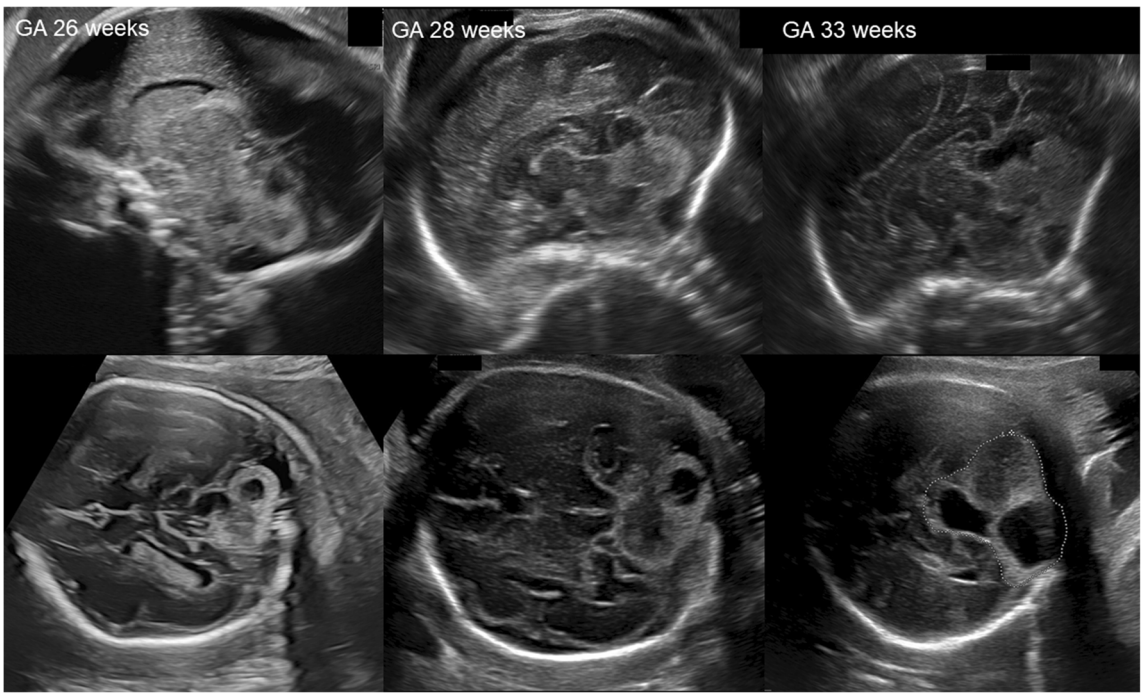

Fig. 1 Serial antenatal fetal ultrasonography obtained for the screening test. The upper image is a sagittal view, and the lower image is a coronal view. At gestational age (GA) of 26 weeks, cerebellar dysplasia with hyperechoic cortex involving both vermis and cerebellar hemisphere was observed. The hyperechoic portion grew into a large complex mass containing cysts at 33 weeks. Both cerebellar vermis and hemispheres were involved. Note the enlargement of a hyperechoic mass with cystic structure as time passes

Discussion

Congenital brain tumors are rare and account for less than 2% of pediatric brain tumors [4]. Despite a few previous reports on congenital medulloblastoma, to the best of our knowledge, only two have reported true (i.e., found antenatally) congenital medulloblastomas [5, 6]. MRI in both cases revealed multiple cystic components, as in our case. Both patients presented with obstructive hydrocephalus and IICP signs, and the tumors grew steadily and required surgery [5, 6]. One tumor was diagnosed as a desmoplastic/nodular subtype, and the other report did not provide subtype information. The patient in the desmoplastic/nodular subtype case survived to the time of the report without recurrence, but the patient in the other case expired of the disease [5, 6].

Our case is intriguing in some aspects. First, the tumor showed transient but spontaneous regression after birth. Spontaneous tumor regression has been reported in many brain tumors, most of which are low-grade tumors, such as pilocytic astrocytoma [7]. However, the spontaneous regression of high-grade brain tumors is exceedingly rare, and little is known about medulloblastoma. While the mechanism has to be elucidated, we could make inferences from an experimental animal model. *Smoothened (Smo) A2* transgenic mice, which highlights a key transducer of the SHH pathway, was characterized, and cerebellar developmental dysplasia but normal neurological function of the mice were reported [8]. Interestingly, progenitor cells of the developing cerebellum had neoplastic characteristics morphologically and functionally and had shown apparent regression of the hypercellularity in *SmoA2* mice [8].

Second, the baby did not show abnormal signs or developmental delay. The tumor behaved as if it was supposed to be there since the first detection. The "true" congenital medulloblastomas in the literature were all detected between late 20 and early 30 weeks of GA. This is when the cerebellum

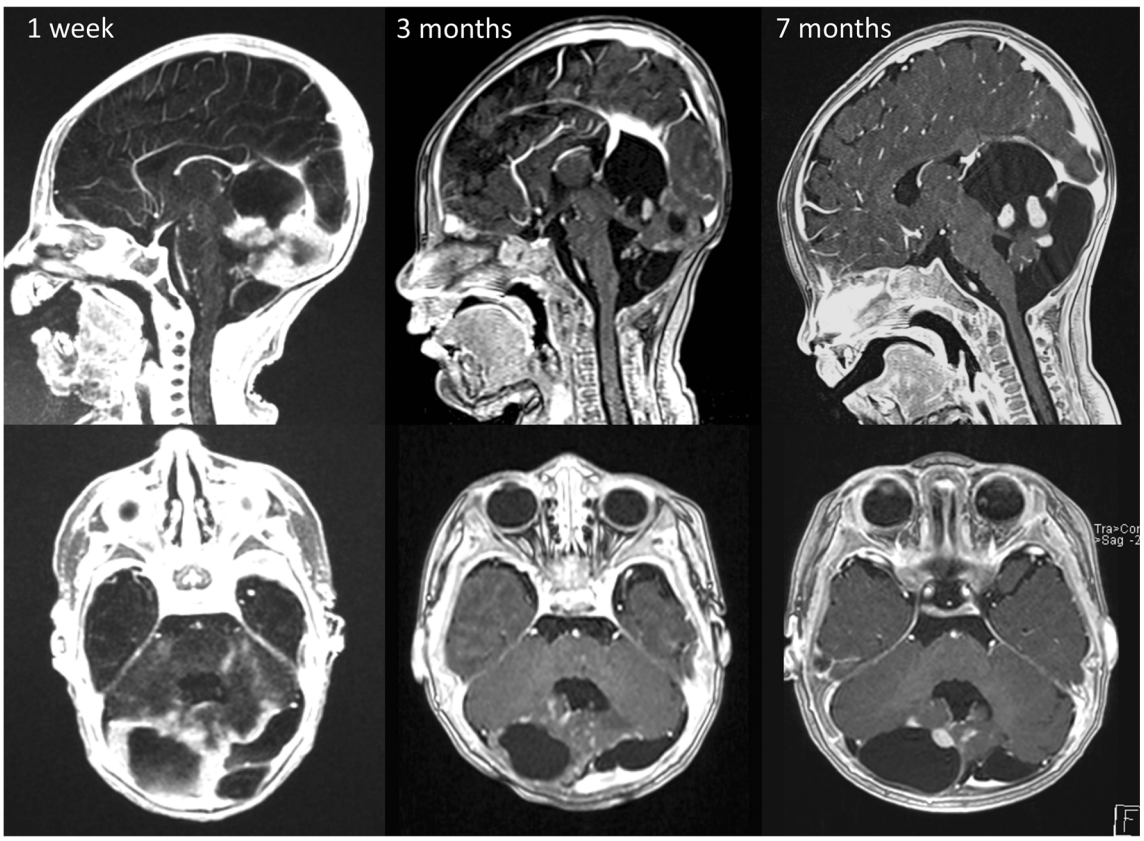

Fig. 2 Serial brain MRI scans obtained throughout the hospitalization course. The upper image is a sagittal view, and the lower image is an axial view. T1 MRI with contrast enhancement showed gadolinium-enhancing infiltrative lesions along the cerebellar folia accompanied by three cysts at 10 days after birth. The demarcation between the tumor and normal parenchyma was not clear. At 3 months of age, a decreased extent of enhancing solid portions with stippled enhancement through the cerebellar surface was noted. MRI at the age of 7 months showed enlargement of both enhancing solid and cystic portions

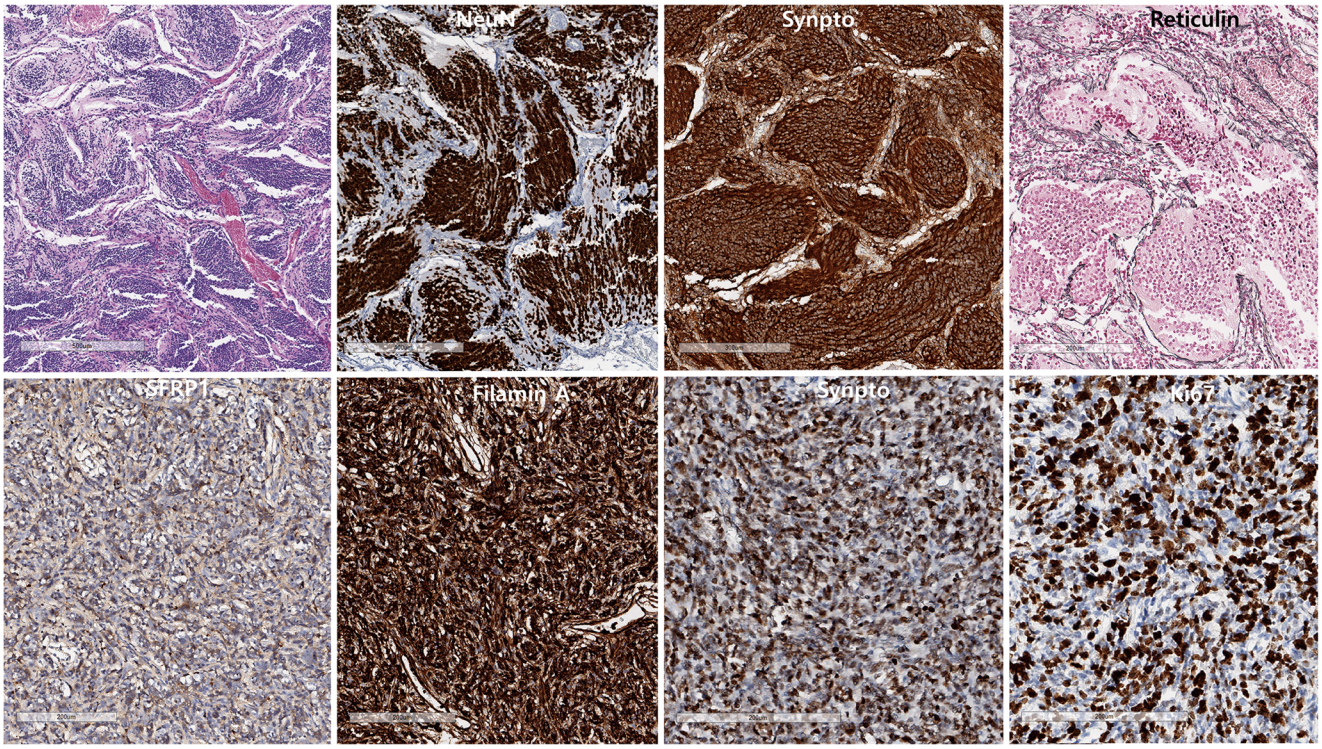

Fig. 3 **a** The histological subtype of this tumor was medulloblastoma with extensive nodularity. **b**, **c** The tumor cells of the nodules were positive for NeuN and synaptophysin, suggesting neuronal differentiation. **d** The nodules were surrounded by thin layers of reticulin fibers, but inside the nodule was free of reticulin. **e**–**g** Some areas did not have nodules but showed a sheetlike growth pattern. The tumor cells in these sheetlike areas were positive for SFRP1, filamin A and synaptophysin. **h** The Ki67 labeling index was high (84.5%). (**a** H&E, **b** NeuN, **c** and **g** synaptophysin, **d** reticulin, **e** SFRP1, **f** filamin A, **h** Ki-67 immunohistochemistry)

significantly expands during organogenesis [9]. Therefore, in our case, the tumor may "literally" be an embryonic tumor that developed together with the cerebellum. Aberrant SHH signaling during development has been presented as the evidence of prenatal origin of medulloblastoma [9].

Third, the tumor showed CDH 1 mutation which has been rarely reported in medulloblastoma. A genomic landscape of 79 medulloblastomas revealed two missense mutations in *CDH1* [10]. *CDH1* gene encodes epithelial cadherin or E-cadherin, which is an important molecule in cell adhesion and stability of epithelial tissue [11]. Comprehensive studies are needed to explore the association between CDH 1 and medulloblastoma.

We report a case of congenital medulloblastoma that showed spontaneous albeit transient regression. This case provides an unusual chance of observing an early phase of medulloblastoma development and raises a suspicion that medulloblastoma may initiate itself early in cerebellar organogenesis and progress later at a time of postnatal development.

Table 1 List of comprehensive gene panel of 72 genomic alterations

ADGRB3	BRCA1	FGFR1	KIT	NOTCH1	ROS1
ADGRG4	BRCA2	FGFR3	KMT2C	NOTCH2	SMARCA2
AKAP6	CDH1	FGFR4	KMT2D	NRAS	SMARCB1
ALK	CDKN1A	GFI1	KRAS	PDGFRA	STAG2
APC	CDKN2B	GLI1	MAPK1	PDGRB	STAT6
ARID1A	DDX3X	GSE1	MAPK3	POLE	SUFU
ARID1B	DICER1	H3F3A	MET	PTCH1	TCF4
ARID2	EGFR	HIST1H3B	MN1	PTCH2	TERTp
ATM	EPHA7	HRAS	MTOR	PTEN	TP53
ATRX	FBFR1	IDH1	MYCN	PTPN11	TSC1
BCOR	FGF3	IDH2	NF1	RB1	TSC2
BRAF	FGF4	JUN	NF2	RET	YAP1

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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